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īS	13	APR	02	EMBASE Adds Unique Records from MEDLINE, Expanding Coverage back to 1948												
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-				available after July 30, 2010												
				DWPI: New coverage - French Granted Patents												
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IS	21	JUN	21	Removal of Pre-IPC 8 data fields streamline displays in CA/CAplus, CASREACT, and MARPAT												
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īS	24	JUN	29	Patenting and Commercialization of Bioethanol Enhanced Batch Search Options in DGENE, USGENE, and PCTGEN												
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FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 12:32:32 ON 29 JUN 2010 200481 S (GROWTH(W) HORMONE OR GH)

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L4 4 DUP REM L3 (3 DUPLICATES REMOVED)

L5 1 S L2 AND (GH_CP0?)

L6 1 S L2 AND (ILE121 OR GLU118)

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L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:34776 CAPLUS

DOCUMENT NUMBER: 142:127937

TITLE: Modified cytokine ligand polypeptides preparation, screening, and uses thereof for treatment INVENTOR(S): Sayers, Jon; Artymmük, Peter; Ross, Richard

PATENT ASSIGNEE(S): Asterion Limited, UK

SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| | PATENT NO. | | | | | | | | | APPLICATION NO. | | | | | | | | | | |
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| | WO | 2005 | 0031 | | A2 | | 20050113 | | | WO 2 | 004- | | 20040628 | | | | | | | |
| | WO 2005003165 | | | | | A3 20050714 | | | | | | | | | | | | | | |
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| | CA | 2568 | 859 | | | A1 | | 2005 | 0113 | | CA 2 | 004- | 2568 | 859 | | 2 | 0040 | 628 | | |
| | ΕP | EP 1639002 | | | | | | 2006 | 0329 | | EP 2004-743175 | | | | | | 20040628 | | | |
| | ΕP | 1639 | 002 | | | B1 | | 2010 | 0505 | | | | | | | | | | | |
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| US 20070264234 | | | | | | A1 | | 20071115 | | | US 2007-561831 | | | | | 20070316 | | | | |
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| | | | | | | | | | | | WO 2 | 004- | GB28 | 27 | | W 2 | 0040 | 628 | | |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The disclosed invention describes modified cytokine ligand polypeptides comprising a modified amino acid sequence which is a modification of the native cytokine amino acid sequence of said ligand, wherein the native N terminal and C terminal amino acid residues of the native polypeptide are linked, directly or indirectly, together, characterized in that said ligand is provided with alternative N terminal and C terminal amino acid residues and further wherein at least one binding domain for said ligand's cognate binding partner or receptor complex is disrupted. The authors describe the first embodiment of the growth hormone circular permutation GR CPOI, with

the N terminus Ile121 and the C terminus Glull8. The "old" termini of

GH were linked by a 6 amino acid linker, formed by joining the "old" termini -3 amino acids from the first helix at the N terminus and +3 residues for the last helix at the C terminus. E. coli cells were used as

the expression system. Also described are alternative approaches to

construct circular permutations of GH. OS.CITING REF COUNT: 2

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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD, ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ANSWER 1 OF 1 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:34776 CAPLUS

DOCUMENT NUMBER: 142:127937

TITLE: Modified cytokine ligand polypeptides preparation,

screening, and uses thereof for treatment INVENTOR(S): Sayers, Jon; Artymuik, Peter; Ross, Richard

PATENT ASSIGNEE(S): Asterion Limited, UK

PCT Int. Appl., 45 pp. SOURCE:

CODEN: PIXXD2 DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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163900 | 2 | | | | | | CA 2004-2568859
EP 2004-743175 | | | | | | | | | | |
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| AT 4 | 166880 |) | | T 20100515 | | | | JP 2006-518330
AT 2004-743175
US 2007-561831 | | | | | | 20040628 | | | | |
| PRIORITY | US 20070264234 A1 20071115 US 2007-561831 20070316 PRIORITY APPLN. INFO.: WO 2004-GB2827 W 20040628 | | | | | | | | | | | | | | | | | |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT The disclosed invention describes modified cytokine ligand polypeptides comprising a modified amino acid sequence which is a modification of the native cytokine amino acid sequence of said ligand, wherein the native N terminal and C terminal amino acid residues of the native polypeptide are linked, directly or indirectly, together, characterized in that said ligand is provided with alternative N terminal and C terminal amino acid residues and further wherein at least one binding domain for said ligand's cognate binding partner or receptor complex is disrupted. The authors describe the first embodiment of the growth hormone

circular permutation GH CP01, with the N terminus Ile121 and the C terminus Glu118. The "old" termini of GH were linked by a 6 amino acid linker, formed by joining the "old" termini -3 amino acids from the first helix at the N terminus and +3 residues for the last helix at the C terminus. E. coli cells were used as the expression system. Also described are alternative approaches to construct circular permutations of GH.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD

(2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 12:32:32 ON 29 JUN 2010

L1 200481 S (GROWTH(W) HORMONE OR GH)

L2 553 S L1 AND (CIRCULAR? OR CIRCULAR(W)PERMUTATION)
L3 7 S L2 AND (SITE(W)2)

L4 4 DUP REM L3 (3 DUPLICATES REMOVED) L5 1 S L2 AND (GH CP0?)

L6 1 S L2 AND (ILE121 OR GLU118)

=> dis ibib abs 14 1-4

L4 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2003280919 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12682073

TITLE: Identification of residues outside the two binding sites that are critical for activation of the lactogenic activity

of human growth hormone.

AUTHOR: Duda Karen M; Brooks Charles L

CORPORATE SOURCE: Ohio State Biochemistry Program, Columbus 43221, USA.
SOURCE: The Journal of biological chemistry, (2003 Jun 20) Vol.

SOURCE: The Journal of biological chemistry, (2003 Jun 20) Vol. 278, No. 25, pp. 22734-9. Electronic Publication:

2003-04-07.

Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: PDB-1A22; PDB-1BP3; PDB-1HGU; PDB-1HWG; PDB-1HWH; PDB-3HHR

ENTRY MONTH: 200308

ENTRY DATE: Entered STN: 17 Jun 2003 Last Updated on STN: 22 Aug 2003

Entered Medline: 21 Aug 2003

AB Human growth hormone (hGH) binds lactogenic or somatotrophic receptors, creating active heterotrimeric complexes. Comparison of hGH structures, either free or bound to a single lactogenic or somatotrophic receptor, shows binding is associated with structural changes. Changes in hGH structure are unique when binding either lactogenic or somatotrophic receptors and they influence the spatial arrangement of residues constituting the second receptor-binding site. Using site-directed mutagenesis, we identified a contiguous set of largely hydrophobic residues that forms a motif communicating between the two receptor-binding sites of hGH. The residues are external to the receptor-binding sites of hGH. The residues are external to the site 2 function without changing site 1 function. The motif includes Phe44, Leu93, Tyr160, Leu163, and Tyr164, located in two hydrophobic clusters between the receptor-binding sites. Their mutation

to Glu disrupts hydrophobic interactions and reduces lactogenic activity between 4.7- and 83-fold with little effect on somatorophic activity or spectroscopic properties. These differential effects indicate that loss of lactogenic activity is not a result of global mis-folding. We propose the loss of lactogenic activity results from disruption of specific hydrophobic clusters that disables the site 1 binding-induced structuring of the second receptor-binding site.

L4 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 1998298111 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9632658

TITLE: Novel recombinant analogues of bovine placental lactogen.

G133K and G133R provide a tool to understand the difference

between the action of prolactin and growth

hormone receptors.

AUTHOR: Helman D; Staten N R; Grosclaude J; Daniel N; Nespoulous C;

Djiane J; Gertler A

CORPORATE SOURCE: Institute of Biochemistry, Food Science and Nutrition,
Faculty of Agriculture, The Hebrew University of Jerusalem,

Rehovot 76100, Israel.

SOURCE: The Journal of biological chemistry, (1998 Jun 26) Vol.

273, No. 26, pp. 16067-74.

Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 17 Aug 1998

Last Updated on STN: 17 Aug 1998 Entered Medline: 3 Aug 1998

Two new analogues of bovine placental lactogen (bPL), bPL(G133K) and AB bPL(G133R), were expressed in Escherichia coli, refolded, and purified to a native form. Binding experiments, which are likely to represent the binding to site 1 only, to intact FDC-P1 cells transfected with rabbit (rb) growth hormone receptor (GHR) or with human (h) GHR, to Nb2 rat lymphoma cells, or to rabbit mammary gland membranes prolactin receptor (PRLR), revealed only small or no reduction in binding capacity. The complex formation between these analogues and receptor extracellular domains (R-ECD) of various hormones was determined by gel filtration. Wild type bPL yielded 1:2 complex with hGHR-ECD, rat PRLR-ECD, and rbPRLR-ECD, whereas both analogues formed only 1:1 complexes with all R-ECDs tested. Real time kinetics experiments demonstrated that the ability of the analogues to form homodimeric complexes was compromised in both PRLR- and GHR-ECDs. The biological activity transduced through lactogenic receptors in in vitro bioassays in rabbit mammary gland acini culture and in Nb2 cells was almost fully retained, whereas the activity transduced through somatogenic receptors in FDC-P1 cells transfected with rbGHRs or with hGHRs was abolished. Both analogues exhibited antagonistic activity in the latter cells. To explain the discrepancy between the effect of the mutation on the signal transduced by PLR versus GHRs we suggest that: 1) the mutation impairs the ability of site 2 of bPL to form a stable homodimeric complex with both lactogenic and somatogenic receptors by a drastic shortening of the half-life of 2:1 complex; 2) the transient existence of the homodimeric complex is still sufficient to initiate the signal transduced through lactogenic receptors

but not through somatogenic receptors; and 3) one possible reason for this difference is that JAK2, which serves as a mediator of both receptors, is already associated with lactogenic receptors prior to hormone

binding-induced receptor dimerization, whereas in somatogenic receptors the JAK2 receptor association occurs subsequently to receptor dimerization.

L4 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 1997363737 MEDLINE DOCUMENT NUMBER: PubMed ID: 9220030

TITLE: Selective modification at the N-terminal region of human

growth hormone that shows antagonistic

activity. AUTHOR: Tchelet A; Vogel T; Helman D; Guy R; Neospouolus C; Goffin

V; Djiane J; Gertler A

CORPORATE SOURCE: Faculte de Medicine Necker, INSERM, Endocrinologie

Moleculaire, Unite 344, Paris, France.

SOURCE: Molecular and cellular endocrinology, (1997 Jun 20) Vol.

130, No. 1-2, pp. 141-52.

Journal code: 7500844, ISSN: 0303-7207, L-ISSN: 0303-7207. Ireland

PUB. COUNTRY:

DOCUMENT TYPE: (IN VITRO)

Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals ENTRY MONTH: 199709

ENTRY DATE: Entered STN: 13 Oct 1997

Last Updated on STN: 13 Oct 1997 Entered Medline: 29 Sep 1997

A new analogue of recombinant human growth hormone

(hGH), hGH des(1-6,14) was expressed in Escherichia coli, refolded and purified to homogeneity. The mutation decreased the hormone's ability to bind lactogenic and somatogenic receptors through its site 1, and almost completely abolished its ability to bind these receptors through site 2, as evidenced by both binding and gel-filtration

experiments. More specifically, the binding to prolactin receptors (PRLRs) from various species or their soluble recombinant extracellular domains (ECDs) was decreased 1.5-4-fold, whereas the binding to hGH receptor (hGHR) was decreased 10-85-fold. These changes caused an almost total loss of hormone agonistic activity in several in vitro bioassays and subsequently, the hGH des(1-6,14) analogue acquired antagonistic properties. This antagonistic activity was dependent upon modification of site 1. In those cases in which the binding was reduced only slightly,

e.g. binding to rabbit PRLRs, hGH des(1-6,14) acted as a strong antagonist, whereas in others in which the binding of site 1 was reduced to a higher degree, such as other PRLRs and, in particular, hGHR, the antagonistic activity was correspondingly weaker. Circular dichroism spectra of the analogue suggested that these changes do not

result from a decrease in overall alpha-helix content, but rather from minor local structural modifications at the N-terminus.

L4 ANSWER 4 OF 4 MEDLINE on STN

ACCESSION NUMBER: 1995096118 MEDLINE PubMed ID: 7798264 DOCUMENT NUMBER:

TITLE: Evidence for a second receptor binding site on human

prolactin.

Goffin V; Struman I; Mainfroid V; Kinet S; Martial J A CORPORATE SOURCE: Laboratory of Molecular Biology and Genetic Engineering,

University of Liege, Sart-Tilman, Belgium. SOURCE:

The Journal of biological chemistry, (1994 Dec 23) Vol. 269, No. 51, pp. 32598-606.

Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.

PUB. COUNTRY: United States DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals ENTRY MONTH: 199501

ENTRY DATE: Entered STN: 15 Feb 1995

Last Updated on STN: 6 Feb 1998

Entered Medline: 24 Jan 1995

AB The existence of a second receptor binding site on human prolactin (hPRL) was investigated by site-directed mutagenesis. First, 12 residues of helices 1 and 3 were mutated to alanine. Since none of the resulting mutants exhibit reduced bioactivity in the Nb2 cell proliferation bioassay, the mutated residues do not appear to be functionally necessary. Next, small residues surrounding the helix 1-helix 3 interface were replaced with Arg and/or Trp, the aim being to sterically hinder the second binding site. Several of these mutants exhibit only weak agonistic properties, supporting our hypothesis that the channel between helices 1 and 3 is involved in a second receptor binding site. We then analyzed the antagonistic and self-antagonistic properties of native hPRL and of several hPRLs analogs altered at binding site 1 or 2. Even at high concentrations (approximately 10 microM), no self-inhibition was observed with native hPRL; site 2 hPRL mutants self-antagonized while site 1 mutants did not. From these data, we propose a model of hPRL-PRL receptor interaction which slightly differs from that proposed earlier for the homologous human growth hormone (hGH) (Fuh, G., Cunningham, B. C., Fukunaga, R., Nagata, S., and Goeddel, D. V., and Well, J. A. (1992) Science 256, 1677-1680). Like hGH, hPRL would bind sequentially to two receptor molecules, first through site 1, then through site 2, but we would expect the two sites of hPRL to display, unlike the two binding sites of hGH, about the same binding affinity, thus preventing self-antagonism at high concentrations.